REMARKS

Status of the Claims

Claims 1, 5-7, and 9-15 are pending in the present application. Claims 9-15 are withdrawn as directed to a non-elected invention. Claim 1 is amended to incorporate the features of claim 4, now canceled. Claims 2-3 and 8 were previously canceled. No new matter is added by way of this amendment. Reconsideration is respectfully requested.

Rejection Under 35 U.S.C. § 112, First Paragraph

Written Description

Claims 1 and 4-7 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement, *see* Office Action, pages 2-7. Applicants respectfully traverse.

Basis for the rejection

The Examiner states that the specification does not contain any disclosure of the structure and function of all fusion protein constructs comprising pyrroloquinoline quinone glucose dehydrogenase (PQQGDH). The Examiner further states that there is no art-recognized correlation between any structure of a fusion protein and the sequence of SEQ ID NO: 2, wherein such fusion proteins have the desired glucose dehydrogenase activity and an electron transfer ability. According to the Examiner, those of ordinary skill in the art would not be able to identify, without further testing, what specific DNA sequence can be prepared that would encode the desired fusion protein having glucose dehydrogenase activity and an electron transfer ability.

In response to Applicants' previous arguments, the Examiner states that while enzymatic assays are well known in the art, and the skilled artisan can produce variants of the polypeptide of SEQ ID NO: 2 having the recited structural characteristics using well-known and widely used techniques in the art, the amount of experimentation required is not routine due to the fact that the number of species encompassed by part (b) of claim 1 is extremely large.

The Examiner cites Guo *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, 2004, 101(25);9205-9210 (Guo) for the proposition that the percentage of random single substitution mutations, which

inactivate a protein (3-methyladenine DNA glycosylase) is 34% (x factor). The Examiner states that this number appears to be consistent for other proteins. The Examiner further asserts that the teachings in Guo indicate that to find a single active mutant, within random mutants having 95% identity to SEQ ID NO: 2, one of skill in the art would have to screen over several million mutants. The Examiner states that the level of unpredictability can only be imagined if the entire sequence of SEQ ID NO: 2 is modified as encompassed by the language of claim 1(b).

The Claims Comply With the Written Description Requirement

The Claimed Invention

As amended, claim 1 is directed to a fusion protein of pyrroloquinoline quinone glucose dehydrogenase (PQQGDH) and a cytochrome, wherein the cytochrome has been fused to the C-terminal side of PQQGDH, and wherein the PQQGDH is either (a) or (b): (a) a protein comprising an amino acid sequence represented by SEQ ID NO: 2; (b) a protein comprising an amino acid sequence in which one or more amino acid residues have been deleted, substituted or added in the amino acid sequence (a) and having a glucose dehydrogenase activity and an electron transfer ability, and wherein the cytochrome is cytochrome c or cytochrome B562.

Gao does not apply to the fusion protein of SEQ ID NO: 2.

Applicants submit that the teachings in Guo do not establish that the instant amended claims fail to comply with the written description requirement. Applicants note that the Guo document only calculates the "x factor" for AAG. Accordingly, Applicants submit that the results described in Guo do not apply to SEQ ID NO: 2 of the instant claims.

In particular, the authors in Guo state that "[w]e advance the concept of the x factor as a measure of protein tolerance to random substitutions....It may be of particular interest to examine x factors from various protein families and diverse organisms", *see* page 9201 of Guo, right column. The authors further discuss the effects of variable x factors, for example, when x = 1, see page 9209, right column of Guo. In view of the Guo disclosure as a whole, Applicants submit that the Guo authors suggest that the x factor is not 34% for every amino acid sequence. Accordingly, the data described in Guo cannot be applied to the amino acid sequence of instant SEQ ID NO: 2. Therefore, an alleged lack of compliance with the written description requirement is not established by the Guo reference.

An ordinary artisan could have envisioned the SEQ ID NO: 2 variants having the desired activities.

Applicants further submit that an ordinary artisan could have envisioned those variants of SEQ ID NO: 2, encompassed by the pending claims, which would retain glucose dehydrogenase activity and an electron transfer ability from the art known at the time of the invention.

As noted in the response submitted on November 29, 2010, the descriptive text in the specification needed to meet the written description requirement, varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science, *see Falkner v. Inglis*, 448 F.3d 1357, 79 USPQ2d 1001 (Fed. Cir. 2006).

In the instant case, an ordinary artisan would have recognized that the PQQGDH enzyme described in the pending claims belongs to a family of well-characterized proteins. Accordingly, in contrast to the Examiner's assertions, an ordinary artisan would not need to randomly mutate and test variants of SEQ ID NO: 2 to find those, which would retain glucose dehydrogenase activity and electron transfer ability. As evidenced by Exhibits A1-A3, B1-B10, and C1-C16, submitted with the response of November 29, 2010, an ordinary artisan was well aware of the residues in PQQGDH, which are responsible for catalytic activity and/or substrate specificity, *see also* Sode Declaration, enclosed. Accordingly, an ordinary artisan could have envisioned those variants encompassed by the claims, which retain the desired function.

The Sode Declaration provide further evidence that Applicants were in possession of the claimed invention at the time of the filing.

Moreover, as stated in the Sode Declaration, *enclosed*, (executed Declaration will be submitted in a Supplemental Reply), the knowledge in the art at the time of the invention, as evidenced by Exhibits A1-A3, B1-B10, and C1-C16, indicate that an ordinary artisan could have readily envisioned and prepared a variety of PQQGDH mutants having both glucose dehydrogenase activity and electron transfer ability. Further, the structure-function relationship

of PQQGDH and the specific amino acid residues involved in the catalytic activity and/or substrate specificity were already known in the art. Thus, those of ordinary skill in the art could easily prepare a variety of mutants having glucose dehydrogenase activity and electron transfer ability, not by searching from an indefinite number of mutants as the Examiner asserts, but by selecting specific mutants based upon the knowledge of the structure-function relationship.

As indicated in *Falkner, supra,* there is no *per se* requirement that information known in the art at the time of filing be repeated in a specification. As stated above, the descriptive text in the specification needed to meet the written description requirement varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. Accordingly, the claims comply with the written description requirement and withdrawal of the rejection is respectfully requested.

Enablement

Claims 1 and 4-7 are also rejected under 35 U.S.C. § 112, first paragraph, because the claims allegedly fail to comply with the enablement requirement, *see* Office Action, pages 7-10. In response to Applicants' previous arguments, the Examiner states that while enzymatic assays are well known in the art, and the skilled artisan can produce variants of the polypeptide of SEQ ID NO: 2 having the recited structural characteristics using well-known and widely used techniques in the art, the amount of experimentation required is not routine due to the fact that the number of species encompassed by part (b) of claim 1 is extremely large.

The Examiner cites Guo *et al.*, *PNAS*, 2004, 101(25);9205-9210 (Guo) for the proposition that the percentage of random single substitution mutations, which inactivate a protein (3-methyladenine DNA glycosylase) is 34% (x factor). The Examiner states that this number appears to be consistent for other proteins. The Examiner further asserts that the teachings in Guo indicate that to find a single active mutant, within random mutants having 95% identity to SEQ ID NO: 2, one of skill in the art would have to screen over several million mutants. The Examiner states that the level of unpredictability can only be imagined if the entire sequence of SEQ ID NO: 2 is modified as encompassed by the language of claim 1(b).

The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art, *see also* MPEP 2164.08.

Applicants submit that Guo fails to establish that the claims do not comply with the enablement requirement. As noted above, Guo does not establish that the x factor of 34% applies to SEQ ID NO: 2 of the present claims.

Further, as noted above, at the time of the invention an ordinary artisan would have recognized from art known at the time of filing which amino acids in SEQ ID NO: 2 could have been altered without a concomitant loss of glucose dehydrogenase activity and electron transfer ability. Accordingly, given the level of knowledge and skill in the art, an ordinary artisan would have been able to practice the invention without undue experimentation, *see also* enclosed Sode Declaration.

In view of the foregoing and the enclosed Sode Declaration, withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendment, remarks and enclosed Sode Declaration, Applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Linda T. Parker, Ph.D., Registration No. 46,046, at the telephone number of the undersigned below to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Director is hereby authorized in this, concurrent, and future replies to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

Dated: JUL 28 2011

Respectfully submitted,

Reg NO.

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Attachment